Dental characteristics of fibrous dysplasia and McCune-Albright syndrome

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Objective. Fibrous dysplasia (FD) is a skeletal disorder often associated with McCune-Albright syndrome, a rare multisystem disorder caused by *GNAS1* gene mutation. FD frequently affects the craniofacial bones, including the maxilla and the mandible; nevertheless, its effects on dental tissues and the implications for dental care remain unclear. The aim of this study was to characterize the dental features associated with FD and the reaction of affected bones to routine dental therapy.

Study design. Thirty-two patients with FD underwent dental evaluation and endocrine testing as part of the diagnosis of FD/McCune-Albright syndrome. Any dental anomalies were recorded, and the associations between endocrinopathies and dental anomalies were analyzed statistically by means of the paired *t* test.

Results. Eighty-four percent had FD in the maxilla and/or mandible; endocrine dysfunction; and/or renal phosphate wasting. The caries index scores were 2.9 (ages 4-17 years) and 9.6 (ages 18-50 years). Malocclusion (81%) and other prevalent dental anomalies (41%) included tooth rotation, oligodontia, and taurodontism. The expansion of the maxilla or mandible by FD did not distort the dental arch curvature, and routine dental therapies such as extractions, restorations, and orthodontic treatment did not exacerbate FD lesions.

Conclusion. Maxillomandibular FD was associated with higher rates of caries and malocclusion than were present in healthy patients. Furthermore, patients with FD did not require special dental management and were able to undergo routine dental care without an exacerbation of FD lesions.

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Fibrous dysplasia (FD) of bone is characterized by the replacement of normal bone and marrow by fibrous tissue, within which irregular trabeculae of woven bone are haphazardly distributed.[1] FD may affect a single bone (called *monostotic FD*) or multiple bones (called *polyostotic FD* [PFD]) and may be associated with endocrinopathies.[2] FD can occur as part of McCune-Albright syndrome (MAS), a rare multisystem disease that was first described as the triad of PFD, *café-au-lait* skin hyperpigmentation, and precocious puberty.[3] MAS is also associated with other endocrine disorders of the pituitary,[4] thyroid,[5] and adrenal glands.[6] Hypophosphatemia and renal phosphate wasting are commonly observed in patients with FD/MAS.[7] Two separate literature reviews of the years 1926 through 1995 revealed only 158 published cases.[8,9] FD in association with *café-au-lait* skin hyperpigmentation but no endocrinopathy is known as Jaffe-Lichtenstein syndrome.[10]

The molecular mechanism responsible for FD/MAS is a postzygotic activating mutation of the *GNAS1* gene that encodes for the Gs_α subunit of the heterotrimeric G protein complex; the result is constitutive activation of the adenylyl cyclase enzyme and overproduction of 3', 5'-cyclic adenosine monophosphate.[11] The most common *GNAS1* gene mutations are a replacement of arginine by either cysteine or histidine at codon 201 (R201C or R201H), but other mutations have also been identified.[8,12] The severity of the disease phenotype is thought to depend on when the mutation occurs during embryogenesis. If the mutation occurs during the for-

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mation of the inner cell mass, all 3 germ cell layers will be affected and the phenotype will be MAS. If it occurs later in development, only 1 or 2 germ cell layers will be affected and the phenotype is less severe. FD is considered a disease of cells of the mesenchymal stem cell/osteoblastic lineage in which excess cyclic adenosine monophosphate impairs the ability of the stem cell to differentiate into a mature functioning osteoblast.[13] However, it is not known how—or even whether—excess cyclic adenosine monophosphate affects the developing tooth, either directly or indirectly.

Craniofacial bones, including the maxilla and the mandible, are commonly affected by FD, often causing disfigurement. However, despite the frequency of craniofacial involvement, the dental features of FD have been poorly characterized, mainly in isolated case reports with sparse information about the effects of FD on dental tissues.[14-17] The development, eruption, and shedding of primary teeth followed by the development and eruption of permanent teeth are sequential events that may be altered by metabolic dysfunction within dental tissues or the presence of bony pathosis within the jaws. It remains unclear whether the presence of FD in the jaws has any effect on tooth development and function.

The typical appearance of patients with FD of the maxillomandibular bones is that of facial asymmetry (Fig 1, *A*), often associated with palatal asymmetry (Fig 1, *D* and *E*). FD is often associated with characteristic *café-au-lait* skin pigmentation (Fig 1, *A*) and rarely with *café-au-lait* pigmentation of the oral mucosa (Fig 1, *B* and *C*). Panoramic radiographic imaging of the jaws and computed tomography have revealed a ground-glass trabeculation that may progress to mixed radiolucent/radiopaque lesions and thinning of the cortical margin (Fig 2, *D*-*F*). The histologic features of FD are site-specific[1]; in the cranial bones, they are pagetoid in nature, whereas in the gnathic bones, they are hypercellular, and in the axial/appendicular skeletons, they have a Chinese-character pattern (Fig 2, *A*-*C*).

The dental management of patients with craniofacial FD is challenging,[16] and the dental community is wary of treating patients with FD/MAS out of concern relating to the postoperative complications and the possibility of exacerbating FD lesions within the jaws.[17] The aim of this study was to better characterize the dental features associated with FD/MAS and to determine the reaction of maxillomandibular FD to routine dental treatment.

MATERIAL AND METHODS

Thirty-six patients diagnosed with FD/MAS gave written informed consent and were subsequently enrolled in an Institutional Review Board–approved study of FD/MAS at the National Institutes of Health (Bethesda, Md). FD was diagnosed by a combination of the results from clinical history, physical examination, radiographic analyses, and lesional bone biopsy with histopathologic and mutation analyses. Testing of the pituitary, thyroid, parathyroid, adrenal, gonadal, and renal functions was performed.

The dental evaluation included extraoral and intraoral examinations, panoramic and intraoral radiographs, and the preparation of maxillomandibular study casts. Because dysplastic changes in the dentin have been reported in a patient with FD,[14] 15 impacted third molars extracted because of clinical or radiologic indications for treatment were analyzed. The first 4 extracted molars were decalcified and examined microscopically; subsequently, 11 molars were sectioned and examined macroscopically. Patients who underwent dental restorations, orthodontic therapy, and minor surgical procedures such as maxillary or mandibular bone biopsy and extraction of wisdom teeth were followed up for a minimum of 12 months. A questionnaire was used to assess postoperative pain, prolonged bleeding, swelling, occlusal changes, orthodontic relapse, or infection to determine the effects of dental therapy on FD. Clinical examination, panoramic radiography, and computed tomography were performed to further assess dental therapy-related bony changes such as the growth/enlargement of FD lesions or the development of malocclusion in the maxilla or mandible.

Dental caries was diagnosed by means of a clinical examination with a sharp dental explorer and by periapical and bite-wing intraoral radiographs. The caries scores were calculated by using the DFT (decayed and filled teeth) index; the usual DMFT (decayed, missing, and filled teeth) index was not used in this study because some of the missing teeth might have been lost for reasons other than caries. Scores on the caries indices were further compared with historical normal scores for patients in the United States published by the World Health Organization.[18-20]

We analyzed associations between endocrinopathies and dental anomalies by using the paired *t* test, the results of which were calculated with the SAS statistical software package (SAS Institute, Inc, Cary, NC).

RESULTS

After undergoing full radiographic testing and technetium (^{99}Tc-MDP) full-body bone scanning, 4 of the 36 original patients evaluated (11%) were excluded because they did not have an FD lesion in any craniofacial bone. The 32 remaining patients with craniofacial FD are the focus of this report. There were 11 males and 21 females, ranging from 4 to 50 years of age (mean, 21.1 years old). Twenty-three patients had PFD,

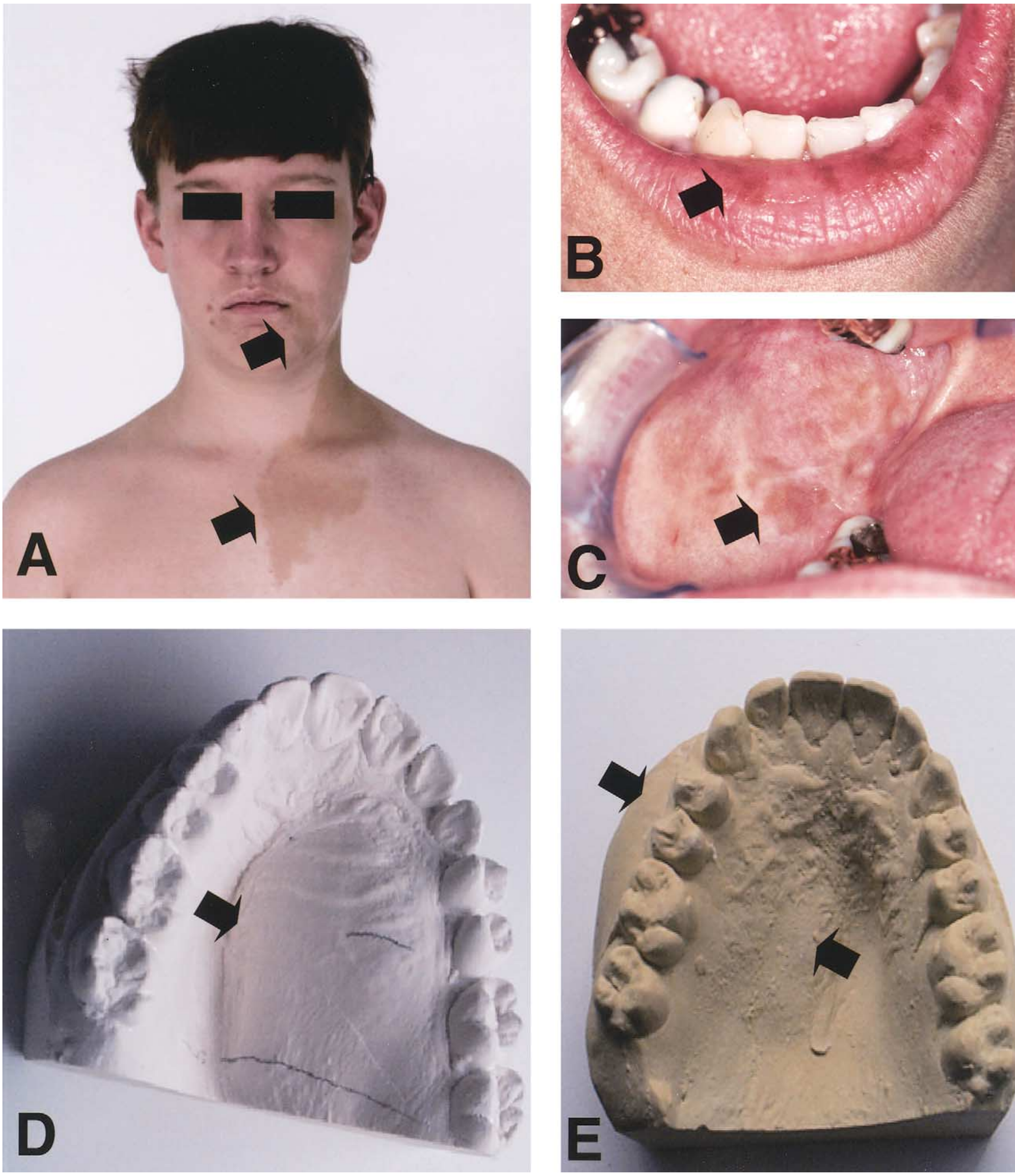

Fig 1. Facial and palatal asymmetries and typical *café-au-lait* pigmentation in patients with fibrous dysplasia (FD) and McCune-Albright syndrome. Note characteristic skin *café-au-lait* pigmentation (hypermelanotic macules) of face and neck (**A**) and rare intraoral *café-au-lait* pigmentation of the lower lip (**B**) and buccal mucosa (**C**). Facial asymmetry can be subtle, as shown in this patient with left maxillary FD (**A**). Despite maxillary and palatal expansions by FD depicted in these maxillary dental casts from 2 separate patients (**D** and **E**), the normal curvature of the maxillary arch is preserved.

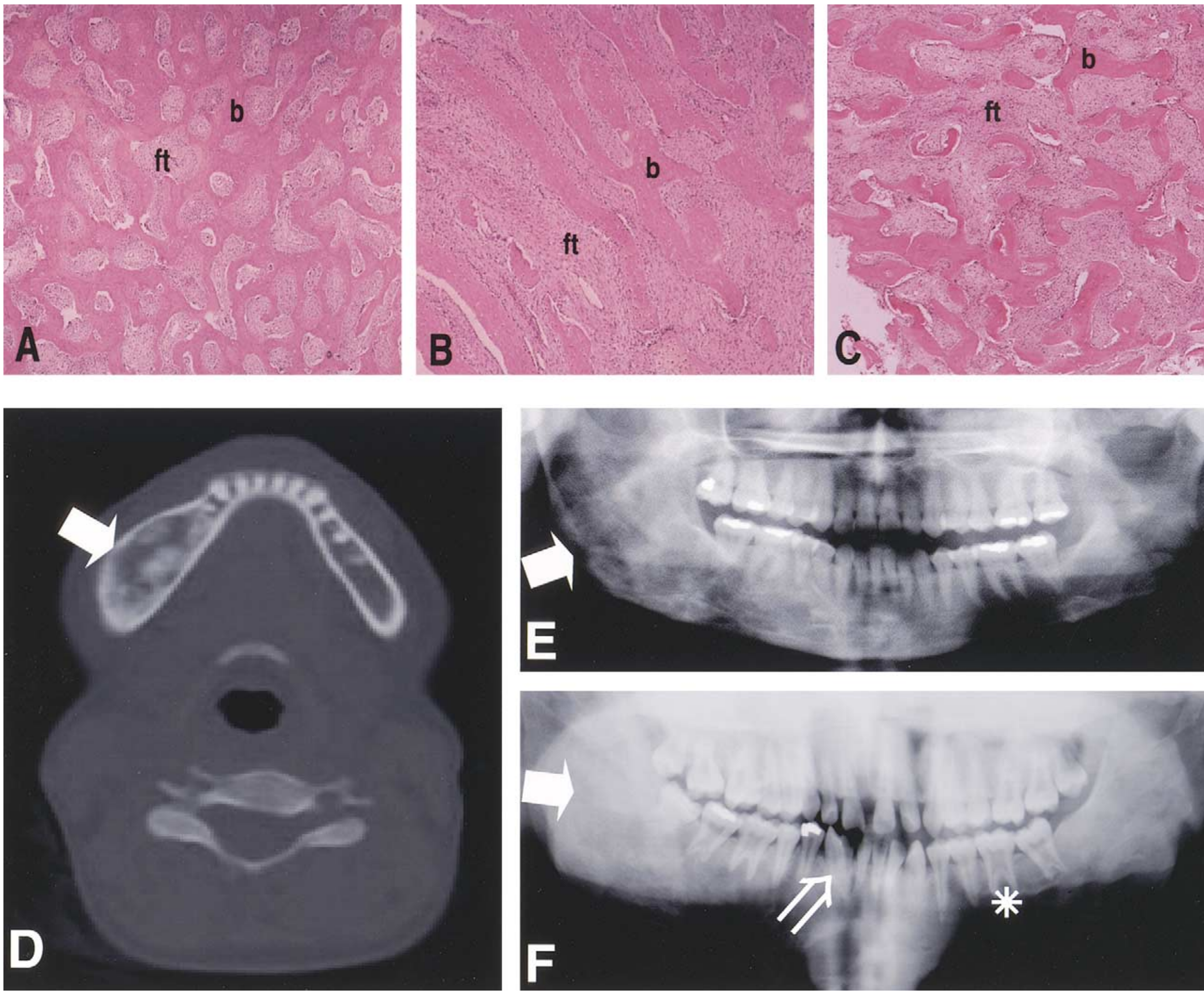

Fig 2. Histologic and radiographic presentations of FD. Different and distinct histologic patterns exist in FD according to the skeletal site of the lesion; generally, craniofacial FD is characterized by an increased amount of bone tissue in comparison with lesions of the appendicular skeleton. In lesions of the cranium (**A**), FD bone is deposited as a continuous system of thick trabeculae enriched in cement lines (sclerotic-pagetoid FD), whereas FD lesions of the maxilla and mandible (**B**) have an evenly oriented bone trabeculae containing an increased amount of osteoblasts and osteocytes (sclerotic-hypercellular). These patterns are clearly distinct from the classic "Chinese-writing" pattern of FD noticeable in appendicular bones (**C**), which is characterized by an abundance of fibrous stroma containing thin and discontinuous bone trabeculae . *b*, Bone; *ft*, = fibrous tissue. A computed tomograph of the mandible (**D**) and panoramic radiographs (**E, F**) of these patients reveal asymmetry and typical sclerotic craniofacial FD marked by high bone content (*solid arrows*). The computed tomograph shows the expansion of the marrow cavity within retained cortices of fibro-osseous tissue (*solid arrow*, **D**). A panoramic radiograph (**F**) was taken of a 15-year-old boy with McCune-Albright syndrome complicated by growth hormone excess; note the extensive radiopacity of FD in both the maxilla and the mandible, the rotation of tooth #27 (*unshaded arrow*), the displacement of tooth #28 and tooth #29, diastemata between teeth #6 to # 11, and taurodontic pulp (*star*) visible in multiple teeth (#2, 3. 14, 15, 18, 19, 30, 31). Pronounced macrocephaly made it difficult to position this patient appropriately in the panoramic radiographic machine.

and 19 of these 23 were diagnosed with MAS on the basis of PFD in association with *café-au-lait* skin pigmentation (Fig 1, *A*) and endocrinopathy or renal phosphate wasting, or both; 14 of these had a combination of 2 or more endocrinopathies or 1 endocrinopathy and renal phosphate wasting (Table I). Precocious puberty, followed by hyperthyroidism and renal phosphate wasting, were the most common abnormalities.

FD was present in the maxilla, mandible, or both in 27 patients (84%) and was frequently associated with malocclusion and palatal, maxillary, or mandibular asymmetry, ranging from mild to severe (Fig 1, *A*, *D*,

Table I. Demographics of clinical findings in patients with fibrous dysplasia

Variables	Age groups (years) 4-17	18-50	Totals
Endocrine dysfunction (no.; %)			
Precocious puberty	11; 55	7; 58	18; 56
Hyperthyroidism	8; 40	5; 42	13; 41
Phosphaturia	9; 45	4; 33	13; 41
GH excess	5; 25	1; 8	6; 19
Hyperparathyroidism	0	1; 8	1; 3
FD in maxilla or mandible (no.; %)	17; 85	10; 83	27; 84
FD in maxilla and mandible (no.; %)	6; 30	4; 33	10; 31
Malocclusion (no.; %)	15; 75	11; 92	26; 81
Jaw asymmetry	14; 70	10; 83	24; 75
Palatal asymmetry	12; 60	7; 58	19; 59
Tooth anomalies	10; 50	3; 25	13; 41
Tooth anomaly in bone with FD	5; 25	4; 33	9; 28
Abnormal TMJ ROM	8; 40	8; 67	16; 50
DFT index scores*	2.9	9.6	N/A

M, Male; *F,* female; *GH,* growth hormone; *FD,* fibrous dysplasia; *TMJ ROM,* temporomandibular joint range of motion; *DFT,* decay and filled teeth; *N/A,* not applicable.
*Calculated on permanent teeth only.

and *E*; Table I). The dental anomalies included rotation, oligodontia, displacement, enamel hypoplasia and hypomineralization, taurodontism, retained deciduous teeth, and attrition (Fig 3). Malocclusion was the most common abnormality, but it did not correlate with the concomitant presence of a tooth anomaly and an FD lesion, observed in the jaws of 9 patients (28%; Table I). Caries scores on the DFT index were 2.9 for patients ages 4 to 17 years and 9.6 for those ages 18 to 50 years. Normal DMFT values reported by the World Health Organization for patients in the United States are 1.7 for ages 5 to 17 years and 6.6 for ages 18 years and older.[18,19]

There was no statistically significant correlation between any specific endocrine dysfunction or renal phosphate wasting and the DFT scores or tooth anomaly; nor was there a statistically significant relationship between renal phosphate wasting and enamel hypoplasia, hypomineralization, or between such wasting and attrition. In addition, the 15 impacted third molars that were extracted were normal radiographically; the first 4 were decalcified and, when examined histologically, were found to be normal. The remaining 11 were not examined histologically. However, the prevalence of oligodontia and retained deciduous teeth suggest that mutation may have prevented the formation of permanent successors.

Because of the gross radiopacity and sclerotic nature of gnathic FD, it was difficult to delineate the outline of the mandibular canal in panoramic radiographs of severely affected mandibles; nevertheless, the vast majority of these patients did not report any paresthesia or dysesthesia. Two patients reported unilateral jaw paresthesia. However, both patients had a history of the surgical removal of FD from the associated nerve sites, so the paresthesia was judged to be a result of postoperative changes. Another patient reported temporomandibular joint pain and clicking, but there were no degenerative or bony changes in the condylar head or glenoid fossa and the temporomandibular range of motion was within normal limits.

Interestingly, there were no changes in maxillary or mandibular FD after dental restorations (20 cases), tooth extractions (6 cases), orthodontic therapy (10 cases), the removal of odontoma (1 case), the removal of a maxillary cyst (1 case), or a diagnostic surgical biopsy of maxilla/mandible for FD (7 cases). Furthermore, there were no observed incidents or reports of prolonged bleeding, pain, or swelling; occlusal changes; or infection after these procedures. In the 10 patients who had undergone orthodontic therapy, the duration of treatment varied from 2 to 4 years and the results were less than satisfactory, with a tendency to relapse necessitating a second orthodontic therapy.

DISCUSSION

The relative rarity of FD/MAS and the clinical heterogeneity of this patient population has resulted in inadequate characterization of the disease with regard to dental tissues and treatment. This study represents the largest group of FD/MAS patients to date in whom the resultant dental characteristics have been described, allowing us to make a number of important observations. First, in patients with craniofacial FD, the maxilla or mandible—or both—is involved 84% of the time. Clinical clues to the presence of FD in the mandible or maxilla are facial or palatal asymmetry, typical *café-au-lait* spots, and a history of endocrine disorders associated with MAS, especially precocious puberty. Conversely, if FD is noted in the maxilla or mandible, associated endocrine disease should be suspected and the appropriate referrals should be made.

We were also able to show that FD is frequently associated with dental anomalies, including rotation, oligodontia, displacement, enamel hypoplasia and hypomineralization, taurodontism, and others. The etiology of these anomalies is not known, but it is possible that they are the result of activating mutations in tooth development either directly (eg, enamel hypomineralization and hypoplasia, oligodontia, attrition), or indirectly because of the proximity of abnormal bone (eg, malocclusion, rotation, displacement, retention of deciduous teeth). Taurodontism, a condition visible radiographically in multirooted teeth and characterized by

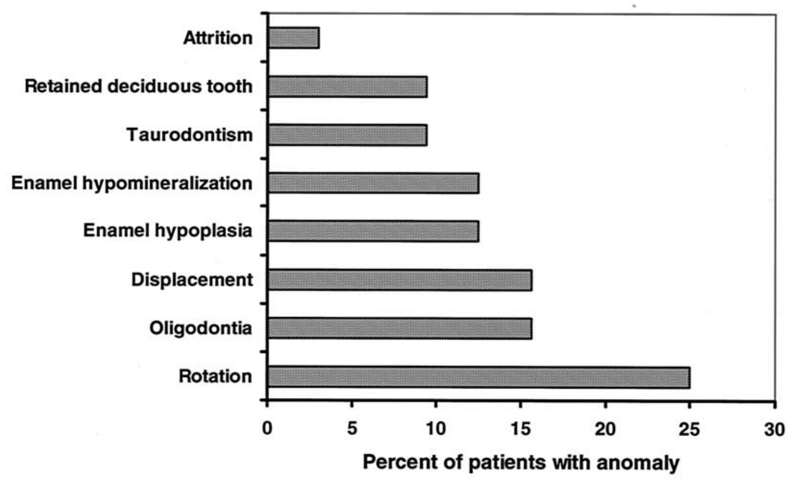

Fig 3. This bar graph depicts prominent dental anomalies identified in patients with maxillomandibular FD.

enlargement of the pulp chamber caused by apical displacement of the bifurcation or trifurcation of the roots, has been described in many syndromes, including patients with growth hormone excess,[21-26] but never in FD/MAS. The incidence of taurodontism observed in this cohort was 9% (3/32) (data not shown). An earlier study associated taurodontism with multiple missing teeth and reported a 34.8% prevalence of taurodontism in subjects with oligodontia compared with 7.5% in a control group.[27] We did not observe an association between oligodontia and taurodontism in our patients. However, the patients with taurodontism were also diagnosed with 1 or more endocrinopathies, including growth hormone excess, precocious puberty, secondary hyperparathyroidism and hyperthyroidism, or renal phosphate wasting. It is possible that the occurrence of taurodontism is attributable to dysregulated endocrine function and/or renal phosphate wasting, because it was found only in patients with these abnormalities; however, it was not possible to determine which abnormality specifically caused taurodontism.

Also of interest are the higher caries index scores in this cohort relative to the normal population. It is possible that associated abnormalities may account for this (especially the propensity for renal phosphate wasting to cause enamel hypoplasia or hypomineralization), but there was no statistically significant relationship between any given endocrinopathy and renal phosphate wasting or between a specific anomaly and an increased caries index score. This may be because of the small number of patients that could be classified into each endocrinopathy or renal phosphate wasting subgroup. Dental caries is caused by multiple factors and missing teeth were not included in calculating the caries index score (DFT) in this study, but the scores of 2.9 and 9.6 for ages 4 to 17 years and 18 to 50 years, respectively, are still higher than normal DMFT values for the US population. Furthermore, if DMFT (instead of DFT) had been calculated, this would have resulted in much higher caries index scores for both age groups. It is possible that the high caries index scores may be attributed to the prevalent enamel hypomineralization and hypoplasia observed or is perhaps the result of suboptimal oral hygiene habits resulting from the maxillary, mandibular, and palatal abnormalities in these patients.

Despite the prevalence of malocclusion, 28% of patients had tooth anomaly in the FD bone. The malpositioned teeth were rotated within the socket or inclined in the mesiodistal direction (Fig 2, *F*); however, no buccolingual displacement or mobility was observed. In essence, the curvilinear pattern of the dental arch was preserved (Fig 1, *D* and *E*). This is in line with the benign nature of FD but contrary to the behavior of other benign lesions such as ossifying fibroma, cementifying fibroma, and aneurysmal bone cyst and the lesions occurring with cherubism, which often cause tooth migration and distortion of the dental arch.[10,28] Furthermore, the patients (for the most part), did not experience any paresthesia or dysesthesia despite extensive involvement of the mandible in some cases. Again, this is in accordance with the nonaggressive behavior reported for FD in the craniofacial region.[29,30] The protracted orthodontic therapy observed may be related to difficulty in tooth movement within sclerotic FD lesions,[1,17] but unlike the results of an isolated case report,[17] the development of a new FD lesion or exacerbation of an existing lesion by orthodontic tooth movement was not observed or reported in our patients.

Of particular importance to the clinician is the lack of complications associated with the routine dental care of patients with FD. We noted no abnormal response or complications in association with dental restorations or extractions. Nor were there any bleeding abnormalities or an exacerbation of the FD in the jaws as a result of routine dental care or after more extensive procedures such as orthodontic movement and even bone biopsy.

Maxillary and mandibular FD is associated with significant facial and palatal asymmetries, heterogeneous dental anomalies, malocclusion, and a high caries index score. The slow progression of FD did not affect vital structures in the maxilla or mandible because there was no significant paresthesia or dysesthesia despite the extensive bony involvement; therefore, surgical intervention was not indicated. These results support those in an earlier report indicating that patients with craniofacial FD were able to maintain normal vision despite encasement of the optic canal in FD, so prophylactic decompression of the optic nerve was unnecessary.[29] For most of the patients with FD, the development and the eruption of the teeth were normal. Malocclusion and caries index scores were higher in patients with maxillomandibular FD, so these patients will benefit from an early orthodontic evaluation and regular, judicious dental care to maintain good oral health. Our study also revealed that dental treatment does not exacerbate FD lesions; in fact, the patients responded normally to routine dental therapies. Nonetheless, orthodontic tooth movement presented a challenge. These patients can be treated as routine dental patients, but dentists should be cognizant that endocrine dysfunction and renal phosphate wasting are common and should consider referral for endocrine testing if the patient has not received testing previously.

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